United States Patent Application No. 09/712,033

EXHIBIT C

A copy of Exhibit C as filed in the July 2004 Amendment is hereby provided.

Efficacy of Crofelemer (SP-303) in Patients with Diarrhea

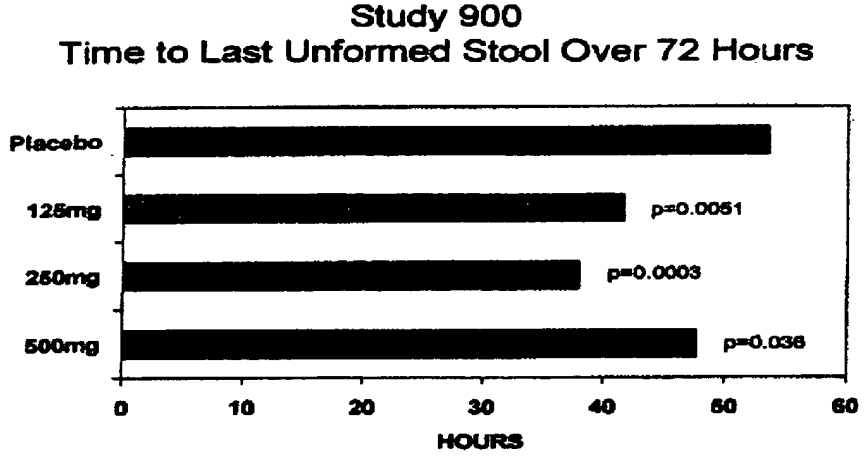
Based on its mechanism of action, i.e., blocking chloride ion secretion through the cystic fibrosis transmembrane conductance regulator (CFTR), crofelemer (previously known as SP-303) was investigated as an agent for the treatment of secretory diarrhea. Crofelemer was evaluated in patients with Traveler's diarrhea (most linked to enteric infections with enterotoxigenic *E. coli* [ETEC]) and HIV-associated diarrhea, which is a more diverse group of patients.

The efficacy data obtained in patients with HIV-associated diarrhea was sufficient to obtain Fast-Track status from the FDA in 1998 and to have that status reaffirmed in a meeting with the FDA in April 2004.

Traveler's diarrhea

A total of 184 patients with traveler's diarrhea or non-specific diarrhea were enrolled in a Phase 2, double-blind, placebo-controlled dose-ranging trial in which crofelemer was given at a dose of 125 mg, 250 mg, or 500 mg qid for 2 days; crofelemer was administered as enteric-coated tablets in capsules. Compared to placebo, all three doses of crofelemer produced a statistically significant beneficial effect, including earlier recovery time (Figure 1), increased number of patients experiencing recovery by 24 hours of treatment (Figure 2), reduction in overall treatment failure rate (Figure 3), and improved symptoms, including abdominal pain and urgency. The results from this study clearly demonstrate the activity of SP-303 and support its use in secretory diarrhea.

Figure 1 **Time to last unformed stool over 72 hours in phase 2 Traveler's diarrhea study 900**



Mean values

Figure 2 **Partial of complete improvement at 24 hours in phase 2 Traveler's diarrhea study 900**

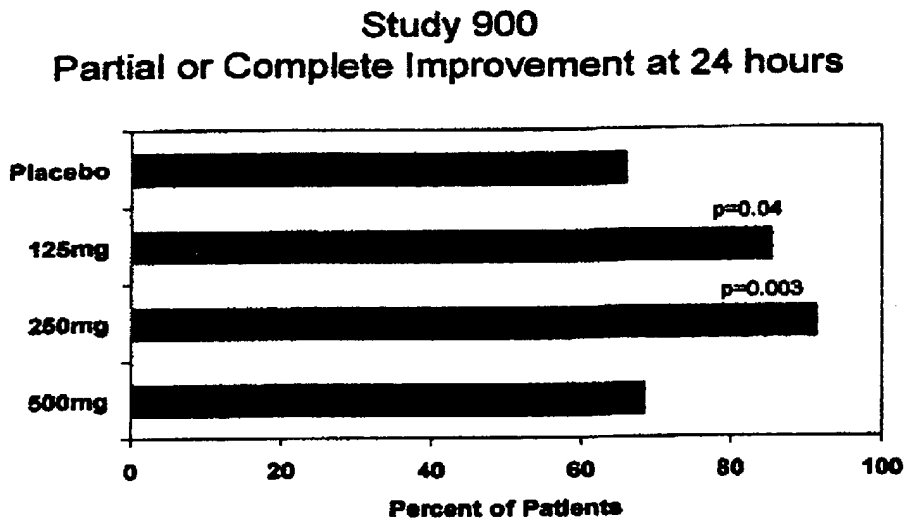
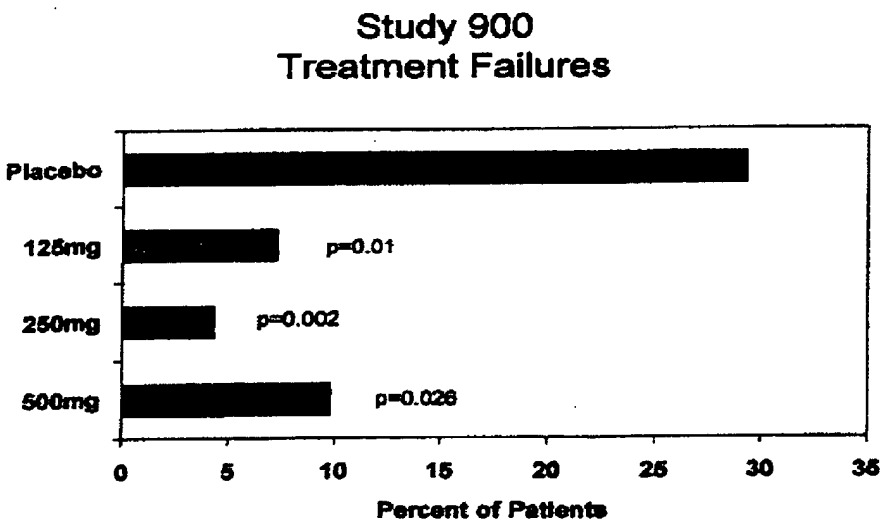


Figure 3 **Treatment failures in phase 2 Traveler's diarrhea study 900**

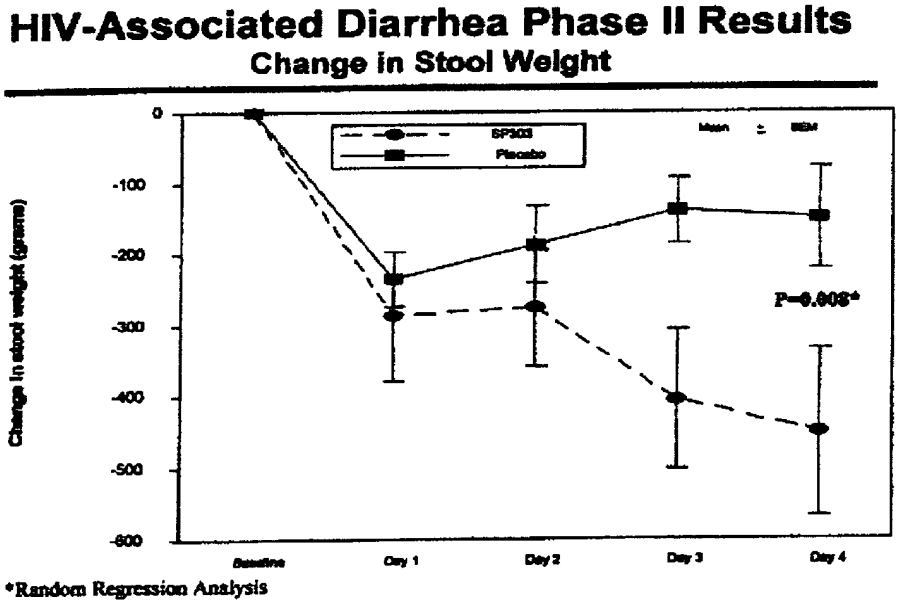


HIV-associated diarrhea

Two studies were conducted with crofelemer in patients with chronic diarrhea associated with HIV/AIDS. In both trials, crofelemer produced clinically relevant decreases in stool weight and decreased stool frequency; significant improvements in gastrointestinal symptoms, particularly urgency, were also associated with crofelemer therapy. Significant reductions in stool chloride concentrations were noted in patients receiving crofelemer, confirming its preclinical mechanism of action.

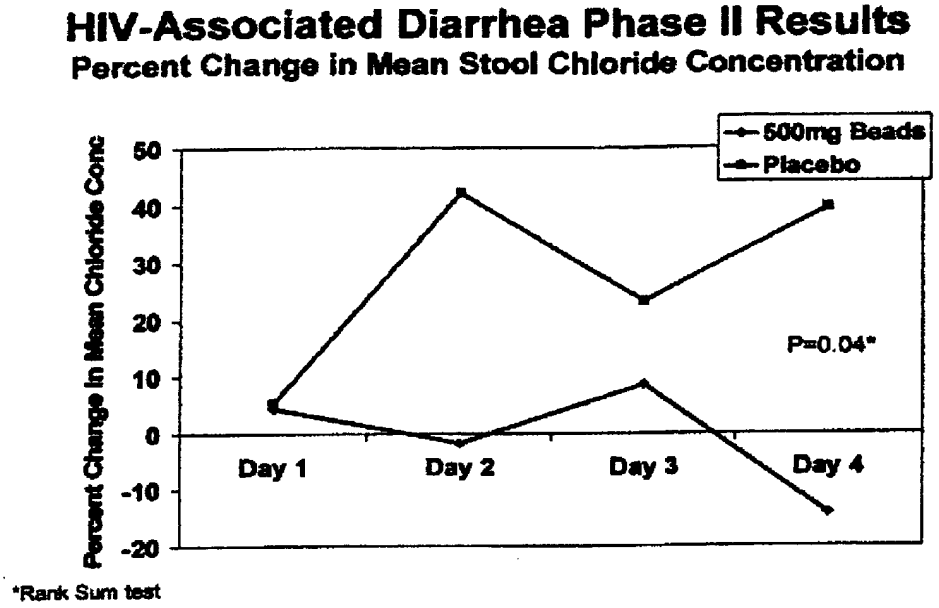
Croflemer was previously evaluated in a phase 2 study in patients with HIV-associated diarrhea entitled "A Double Blind, Randomized, Placebo Controlled, Phase II Study to Assess the Safety and Efficacy of Orally Administered SP-303 for the Symptomatic Treatment of Diarrhea in Patients with AIDS." An enteric coated bead formulation of crofelemer was given at doses of 500 mg qid for 4 days in a hospital inpatient setting. Crofelemer produced a substantial reduction in daily stool weight and frequency by Day 4 (Figure 4). A random regression analysis of slopes revealed statistically significant differences in both stool weight (p=0.008) and in stool frequency (p=0.04) compared to placebo. Significant reductions in stool chloride concentrations compared to placebo were noted in patients receiving crofelemer (Figure 5), confirming its preclinical mechanism of action.

Figure 4 **Change in stool weight in study 37,554-209 (SP-303 500 mg beads versus placebo)**



*Random Regression Analysis

Figure 5 **Percent change in mean stool chloride concentration in study 37,554-209 (SP-303 500 mg beads versus placebo)**

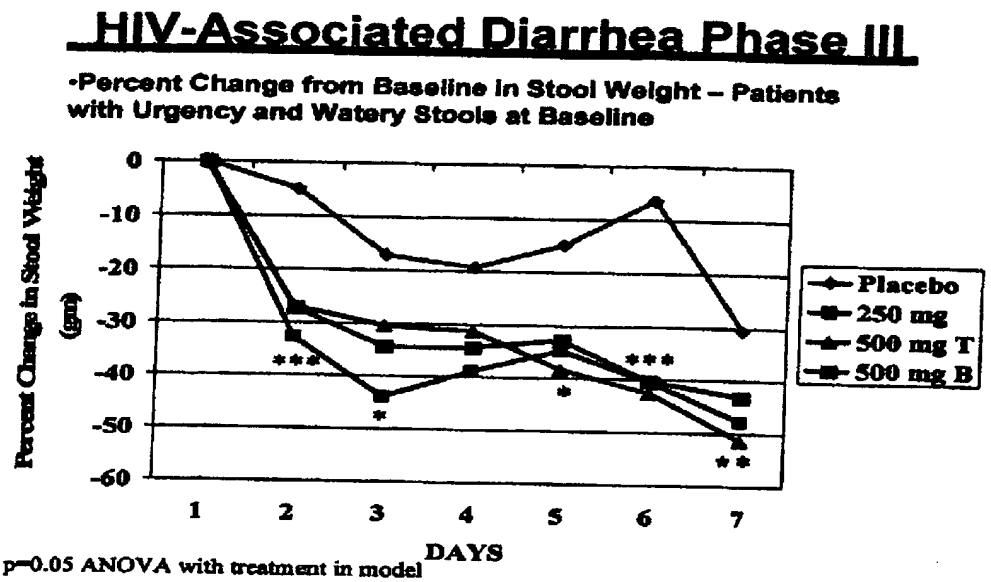


The significant efficacy observed in this phase 2 trial led to a phase 3 study, "A Double Blind, Randomized, Placebo Controlled, Phase III Study to Assess the Safety and Efficacy of Orally Administered SP-303 for the Symptomatic Treatment of Diarrhea in Patients with AIDS." In this study, 400 patients with chronic HIV-associated diarrhea were treated with crofelemer or placebo. Crofelemer was given at doses of 250 mg and 500 mg enteric-coated tablets or 500 mg enteric-coated beads in capsules qid for 6 days in an inpatient setting; patients who responded to treatment were continued in a four-week blinded out-patient phase. In a random regression analysis, the difference between the 500mg tablet group and placebo was significant ($p = 0.03$). Analysis of patients who presented with several watery stools at baseline or who presented with at least one watery stool and an important gastrointestinal symptom demonstrated statistically significant efficacy for crofelemer treatment.

Statistically significant efficacy of crofelemer is also observed in a subset of patients in the ITT population with at least one watery stool and some associated urgency at baseline defined as the "significant baseline diarrhea subset." Urgency was prospectively selected as an important marker of truly symptomatic patients, and was one of the most frequently reported gastrointestinal symptoms in the study. In the patients with watery stools and urgency at baseline, significant reductions in percent change in total stool weight (Figure 6) and abnormal stool weight were observed. In both of these analyses, significant differences between active and placebo arms were observed starting at Day 2. Significant reductions in the frequency of total stools and abnormal stools were also observed in the significant baseline diarrhea subset. The number of patients who continued to experience watery stools on Day 7 was also significantly lower for the 500mg dose arms compared

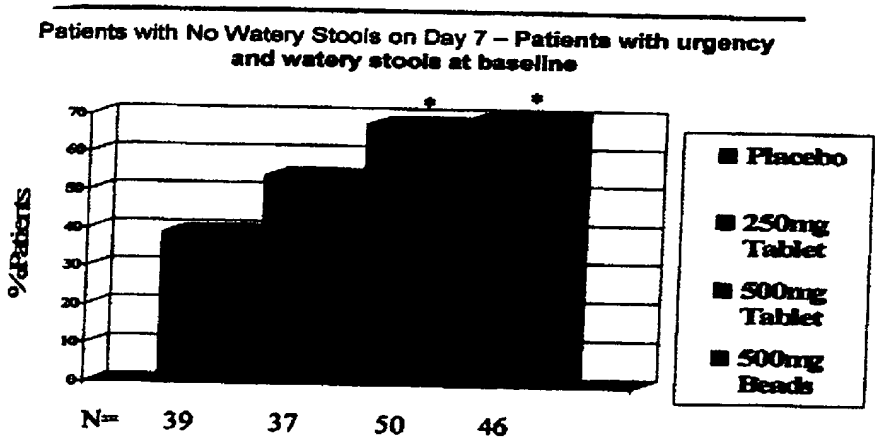
to placebo (Figure 7); confirming that both formulations, which protect crofelemer from the stomach environment, produced equivalent efficacy.

Figure 6 **Percent change in stool weight in significant baseline diarrhea subset in study 37,554-210**



* p=0.05 ANOVA with treatment in model

Figure 7 **Patients with <u>no</u> watery stools on Day 7 in significant baseline diarrhea subset in study 37,554-210**



* p ≤ 0.02; Shaman ITT population